

U.S. Patent Application Serial No. 10/510,619

Reply to Office Action of December 27, 2006

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Applicants have received and reviewed an Office Action dated December 21, 2006. By way of response, Applicants have amended claims 4-21 for editorial purposes and clarity, and have added new claim 22. Support for the new claim can be found at least at page 6, lines 7-9, page 9, lines 14-16, and page 10, lines 27-30.

Applicants have identified the compound corresponding to the HPLC peak described in the specification as having the structure of formula 4. Applicants inherently disclosed this structure by noting its elution time, which is unique to the compound having chemical structure shown in formula 4; thus, disclosing the chemical structure is not an insertion of new matter. Claims 1 to 22 are pending. Applicants submit that the pending claims are supported by the specification.

For the reasons given below, Applicants submit that the amended and newly presented claims are in condition for allowance and notification to that effect is earnestly solicited.

Claim Rejections – 35 USC § 102(b)

Claims 1-7 were rejected under 35 USC § 102(b) as unpatentable over Schumacher et al., WO 99/01450. Although this rejection has not been raised for newly presented claim 22, it is discussed insofar as it might apply. Applicants respectfully traverse this rejection.

The Office Action asserts that Examples 2-4 of Schumacher et al. disclose desloratadine having a purity of 100%. Applicants submit that Schumacher et al. disclose not a chemical purity, but a polymorphic purity as determined by FTIR. The Examiners' attention is directed to Schumacher et al. at page 17, lines 5-6, which discloses that "The white crystalline solid contained 100% of form 1, with no detectable amount of form 2 by FTIR spectrophotometry;" to page 18, lines 2-3, that discloses "polymorph form 1 descarbonylethoxyloratadine [chemical name for desloratadine] (100% by FTIR spectrophotometry) was obtained as a white crystalline solid;" and to lines 15-17 in paragraph 2 on pg 18 that discloses "polymorph form 2 descarbonylethoxyloratadine as a white crystalline solid, having mp 154.0-155.5°C, and containing 100% form 2 by FTIR spectrophotometry." These passages clearly indicate that the

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100% purity is not with regard to other chemical species, but only with regard to other polymorphs of desloratadine.

In contrast, Applicants disclose a chemical purity of desloratadine of greater than 99.5%, determined by HPLC as disclosed in the Examples of the specification. Polymorphic purity and chemical purity are distinct concepts. Polymorphic purity is only a measure of the exclusion of other polymorphs. Substantial impurities that are different chemical species can be present in a material having 100% polymorphic purity. Thus measurement of polymorphic purity does not teach or suggest degree of chemical purity. HPLC does not determine polymorphic purity because HPLC is a solution-based elution test and polymorphs are crystal forms that do not, by definition, exist in solution. Therefore the disclosure of Schumacher et al. does not anticipate Applicants' chemically pure desloratadine of claims 1-7.

Additionally, Applicants note in the specification at page 10, lines 27-30 that preparation of desloratadine was carried out according to the methods disclosed in Schumacher et al. and the resulting material contained the chemical impurity that Applicants eliminated by using the methodologies of the invention. Thus, claims 1-7 are not anticipated by Schumacher et al. Applicants respectfully request withdrawal of the rejection.

Claim Rejections – 35 USC § 103(a)

Claims 1-20 were rejected under 35 USC 103(a) as obvious over Schumacher et al. in view of Villani et al., WO 85/03707. Although this rejection has not been raised for newly presented claim 22, it is discussed insofar as it might apply. Applicants respectfully traverse this rejection.

As described above, Schumacher et al. do not teach or suggest desloratadine having chemical purity of greater than 99.5%, nor do Schumacher et al. teach or suggest a method for making desloratadine having a chemical purity of greater than 99.5%. In Example 2 (page 16) Schumacher et al. teach alkaline hydrolysis of loratadine to prepare descarbonylthoxyloratadine (chemical name for desloratadine). Thus, Schumacher et al. do not teach nor suggest acidic hydrolysis of compound of formula 3 of Applicants' disclosure to result in desloratadine of high chemical purity.

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Schumacher et al. also describe alternative synthetic pathways to desloratadine in Examples 4 and 5. The methods employed are in accordance with Example VI of Villani et al., US 4,659,716. However, Example VI of the '716 patent does not employ acid hydrolysis of Applicants' formula 3, wherein R is selected from COR₁, COOR₁, wherein R₁ is selected from branched or linear alkyl containing 1 to 6 carbon atoms, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl and their substituted analogs. Instead, Example VI of the '716 patent employs 8-chloro-6,11-dihydro-11-(1-cyano-4-piperidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine as the starting material and treats with hydrochloric acid and acetic acid followed by neutralization with ammonium hydroxide and extraction with chloroform to obtain desloratadine.

Villani et al. in WO 85/03707 do not teach or suggest acid hydrolysis as a means of converting the ethoxycarbonyl derivative of desloratadine to desloratadine. Villani et al. instead accomplish this synthetic step employing sodium hydroxide in refluxing ethyl alcohol, followed by acidification and extraction of the final product.

Additionally, Applicants disclose at page 10, lines 27-30 that preparation of desloratadine was carried out according to the methods disclosed in Schumacher et al. and Villani et al. and the resulting material contained the chemical impurity that Applicants eliminated using the methodologies of the invention. Thus, the combination of the cited references would not result in the conversion of a compound of formula 3 to desloratadine having chemical purity of greater than 99.5% via acid hydrolysis. Nor is there anything in either of the cited references suggest Applicants' methods or some other way to reach Applicants' high purity product. Indeed, the synthetic route resulting in the surprisingly high purity of the product discovered by Applicants substantially eliminates a substantial byproduct present in all known prior art methodologies. This unexpected result is further evidence of nonobviousness of the methods employed by Applicants.

The Office Action asserts that it would be *prima facie* obvious to one of skill in the art of process and purification to make a substance acidic then basic to accomplish purification of substances, and thus the motivation to do so exists. Applicants respectfully submit that in taking official notice, it is never appropriate for the Examiner to rely only on common knowledge in the art.

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"It would not be appropriate for the examiner to take official notice of facts without citing a prior art reference where the facts asserted to be well known are not capable of instant and unquestionable demonstration as being well-known. For example, assertions of technical facts in the areas of esoteric technology or specific knowledge of the prior art must always be supported by citation to some reference work recognized as standard in the pertinent art." MPEP § 2144.03.

Thus, such an assertion must be supported by facts, with documentary evidence demonstrating that the asserted facts are well known in the art. The Examiner has failed to provide any documentary evidence that it would have been obvious to one of skill in the art to modify the cited references to reach Applicants' method of synthesizing desloratadine to result in the associated high purity product of the present claims. *See In re Zurko*, 258 F.3d 1379, 1385 (Fed. Cir. 2001) ("[T]he Board cannot simply reach conclusions based on its own understanding or experience—or on its assessment of what would be basic knowledge or common sense. Rather, the Board must point to some concrete evidence in the record in support of these findings.").

Furthermore, where the Examiner takes official notice of a fact unsupported by documentary evidence, the Examiner must provide a technical line of reasoning underlying the decision to take official notice. General conclusions about what is common sense to one of ordinary skill in the art, without specific factual findings or evidence on the record, are not sufficient to support an obviousness rejection.

The Examiner has provided neither evidentiary support for the assertion of *prima facie* obviousness nor a technical line of reasoning supporting the decision to take official notice of what would have been obvious to one of skill in the art. Applicants submit that there is insufficient evidence to support a finding of obviousness. Accordingly, Applicants respectfully request that the rejection be withdrawn.

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In view of the above amendments and remarks, Applicants respectfully request a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

MERCHANT & GOULD P.C.

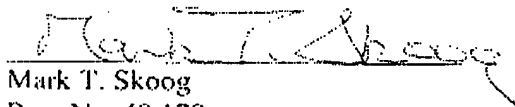
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